Self-Sensitized Photooxidation of Protoporphyrin IX Derivatives in Aqueous Surfactant Solutions: Product and Mechanistic Studies[1,2]

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Abstract: The photooxidation of protoporphyrin IX and its dimethyl ester has been investigated in several aqueous surfactant media including neutral micelles (Brij 35) and vesicles (dipalmitoylphosphatidylcholine) and charged micelles (SDS and DTAB). The results obtained indicate that while the same products are formed in these media as in homogeneous organic solvents such as methylene chloride, the product distributions are quite different. At least two major reaction paths are indicated. The first involves singlet oxygen generation and attack on ground-state porphyrins. This path can be shown by studies with H_2O vs. D_2O and the use of the aqueous phase quencher N_3^- to consist of two components, an intramicellar path and an intermicellar reaction. The second path appears most likely to involve electron transfer from excited porphyrin to generate superoxide and porphyrin π-cation. This path appears to be exclusively intramicellar and is much more prominent in the organized media than in homogeneous solution. Quenching of $^1O_2$* by azide appears to *enhance* the "superoxide-derived" products in SDS and Brij 35 supporting recent studies indicating that azide quenching occurs at least in part by electron transfer.

The relationship between photosensitized oxidations in solution and "photodynamic action" in biological systems remains one of the key questions and areas of investigation in photobiology.[4,5] Recent studies of solution-phase photooxidations have established that several pathways for reaction may be operative for relatively simple systems and that these are quite solvent-sensitive;[6-9] thus it is not terribly surprising that significant differences can occur for a given substrate–sensitizer combination when it is exposed to light in a complex biological environment of variable "solvent" composition which may also include reactive protein or lipid components.[10-17] A number of photooxidations can be initiated by exciting porphyrins such as hematoporphyrin IX and protoporphyrin IX; these compounds are also involved in biological processes ranging from tumor phototherapy to the genetic disorder porphyria.[18-31] Protoporphyrin IX and its various ester derivatives are especially interesting in that the presence of reactive vinyl groups permits this porphyrin to self-sensitize its own photooxidation as well as that of other substrates. We have recently completed a detailed study of the self-sensitized photooxidation of protoporphyrin IX in solution which permitted a delineation of the mechanisms operative for its oxidation and their relative importance.[32] We have also reported preliminary results of a study of the photooxidation of a surfactant derivative of protoporphyrin IX in monolayer films, supported multilayers, and cetyltrimethylammonium bromide (CTAB) micelles.[2]

Table I. Literature Values for the Diffusion of Oxygen in Micelles

media	k_b, M^{-1} s^{-1}	k_Q, s^{-1}	ref
H_2O	5.8×10^9		36
H_2O	1.1×10^{10}		37
SDS	4.8×10^9		36
SDS	9.2×10^9		37
SDS	1.4×10^{10}	5.3×10^7	38
SDS	1.0×10^8	3.7×10^7	39
CTAB	5.2×10^9		36
CTAB	8.3×10^9		37
CTAB	1.3×10^{10}	4.6×10^7	38
Brij 35	2.4×10^9		37

In all media studied thus far the major isolable photooxidation products from protoporphyrin are the hydroxyaldehydes **2** and **3** and the mono and diformyldeuteroporphyrins **4–6** (eq 1).[2,32] It was found that in solution the major portion of all these products is formed by addition of singlet oxygen to ground state protoporphyrin (type II mechanism); the formyl products can be formed via attack of superoxide on porphyrin cation and a minor path for formation of **4–6** in solution may be by this route.[32] Our preliminary studies in monolayer films and supported multilayers indicated a drastic increase in the proportion of the formyl products in the organized assemblies which suggested the possibility that different mechanisms might be operative in these media.[2] In the present paper we report a product and mechanistic study of the

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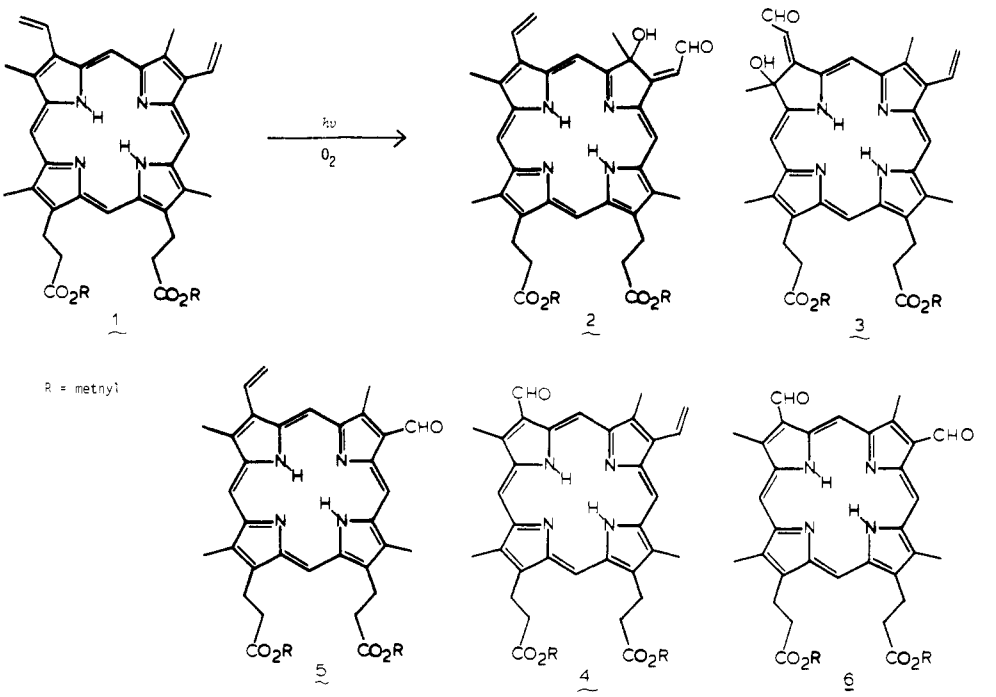

(1)

self-sensitized photooxidation of protoporphyrin in a variety of micellar media and in vesicles. These studies show that there is indeed a substantial change in product distribution which accompanies the change from solution to organized media and that this change can be attributed to the operation of different mechanisms for formation of the various oxidation products.

To understand the nature of photooxidations in biological systems and in organized media, it is important to understand how oxygen diffuses in such systems. Initial studies showed that the fluorescence intensity of compounds solubilized in micelles was higher than in organic solvents.[33] Since oxygen quenches the fluorescence of many compounds, these results were initially interpreted to indicate that the micelle provided a barrier to oxygen diffusion.[34] However, further studies indicated that this effect is due to the lower concentration of oxygen in water as compared to organic solvents.[35] Table I shows the rate constants for diffusion of oxygen into (k_b) and out of (k_0) a micelle.[36-39] In most cases, the rates were determined by studying oxygen quenching of excited states. These data show that the rate of transfer of oxygen from the aqueous phase into a micelle is diffusion controlled and that the rate of escape of oxygen from a micelle is slower than the diffusion into the micelle. This indicates that there is a higher concentration of oxygen in the micelle as compared to its concentration in the bulk aqueous phase. However, there is still some disagreement over the value of this equilibrium constant.

Some studies have already been done on photooxidation in organized media. Kraljic and co-workers have shown that singlet oxygen, sensitized by chlorophyll solubilized in a micelle, will diffuse out of the micelle and react in the aqueous phase.[40] Their results indicated that the quantum yield for diffusion of singlet oxygen out of the micelle (ϕ = 0.7–0.85) was quite high.

1,3-Diphenylisobenzofuran (DPBF) solubilized in micelles has been used extensively to study the properties of singlet oxygen in aqueous solution. Lindig and Rodgers have used this reaction of singlet oxygen with DPBF to determine the lifetime of singlet oxygen in aqueous solutions.[41] In their studies DPBF photooxidation was sensitized by methylene blue dissolved in the aqueous phase or by 2-acetonaphthone which is solubilized in micelles. They determined that the lifetimes of singlet oxygen in SDS micelles (τ^0 = 53 μs) and Brij 35 micelles (τ^0 = 26 μs) dissolved in D_2O were much higher than the lifetime of singlet oxygen in H_2O (τ^0 = 2–3 μs). Lindig and Rodgers also used this same system to determine the rate constants for quenching of singlet oxygen by standard quenchers.[42] They observed that in some cases the rate constant in aqueous solution can be quite different from the value in organic solvents.

Van Ginkel and co-workers have studied the photochemical proton and oxygen uptake by chlorophyll, solubilized in vesicles.[43] They were able to detect superoxide generated photochemically by chlorophyll by spin trapping with DMPO. (DMPO was present in the aqueous phase.) Singlet oxygen was also involved in this system since azide—a standard quencher of singlet oxygen—quenched the reaction.

Schaap and co-workers have studied the photooxidation of cholesterol in dipalmitoylphosphatidylcholine vesicles.[44] If the sensitizer (hematoporphyrin) was solubilized inside the lipid phase of the vesicle, then the quantum yield for the photooxidation of cholesterol was much higher than when the sensitizer was dissolved in the aqueous phase. This difference is due to the longer lifetime of singlet oxygen in the lipid environment as compared to aqueous solution. They also observed that the quantum yield for the photooxidation increases as the temperature increases.[45] This result indicates that the fluidity of oxygen in vesicles is strongly affected by the temperature and whether the vesicle is in the gel or liquid crystalline state. This same result was also observed by Geiger and Turro, with the fluorescence quenching of *trans*-stilbene by oxygen.[46]

Lipids, such as phosphatidylcholine, extracted from biological sources contain some hydrocarbon chains which are unsaturated. These double bonds are susceptible to photooxidation by a variety of sensitizers. Anderson and co-workers have studied the pho-

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tooxidation of such lipids which were incorporated into vesicles.[47] This reaction which was sensitized by toluidine blue O was monitored by following the formation of lipid peroxidases and by eventual lysis of the vesicles. Both β-carotene and diazabicyclo[2.2.2]octane (DABCO) quenched the reaction, indicating the involvement of singlet oxygen.

Micelles can drastically affect the competition between type I and type II oxidation. Jori and co-workers have studied the photooxidation of L-tryptophan and tryptamine sensitized by hematoporphyrin.[48,49] These substrates are photooxidized by both type I and type II mechanisms. In organic solvents type II mechanisms are favored at low substrate concentrations. As the substrate concentration increases, type I mechanisms play a major role, because at higher concentrations substrate quenching of the sensitizer can more effectively compete with oxygen quenching. When the hematoporphyrin-sensitized photooxidation occurred in CTAB micelles the type I pathway was favored even at lower substrate concentration. This result is due to the ability of micelles to complex both the porphyrin and the tryptophan in a small area, thereby increasing the effective concentration. When the reaction occurred in SDS micelles, the type II mechanism was favored because of the separation of the senistizer (micelle) from the substrate (aqueous phase).

Experimental Section

Materials. The synthesis of protoporphyrin IX dimethyl ester, phototoprotoporphyrin IX dimethyl ester, 4(2)-vinyl-2(4)-formyldeuteroporphyrin IX dimethyl ester, and diformyldeuteroporphyrin IX dimethyl ester was previously described.[32] Protoporphyrin IX was synthesized by dissolving protoporphyrin IX dimethyl ester in 25% v/v hydrochloric acid and stirring for several hours. After neutralization with aqueous sodium hydroxide, the crystals were collected and washed with water. Sodium dodecyl sulfate (SDS) (Bio-Rad Laboratories, electrophoresis grade reagent) was recrystallized from absolute ethanol. Brij 35 [polyoxyethylene (23) lauryl ether] (Aldrich) was recrystallized from diethyl ether. Dodecyltrimethylammonium bromide (DTAB, Eastman Kodak) was recrystallized twice from acetone. Dipalmitoyl-L-α-phosphatidylcholine (Sigma), diazabicyclo[2.2.2]octane (Aldrich), and sodium azide (Aldrich) were used as received. Cholesterol (Nutritional Biochemicals Corp.) was recrystallized from 95% ethanol. Deuterium oxide (Merck Sharp and Dohme, 99.7 atom %) was used as received. Water was triply distilled by a procedure described previously.[50] All other solvents were purified by standard distillation procedures.[51]

Formation of Organized Media. Protoporphyrin IX dimethyl ester (**1**) was solubilized into sodium dodecyl sulfate (SDS), DTAB, and Brij 35 [polyoxyethylene (23) lauryl ether] micelles by the following procedure. A 0.065 M surfactant solution (0.1 M in the case of DTAB) was placed into a beaker and stirred with a magnetic stirrer. A 1×10^{-3} M solution of **1** in tetrahydrofuran was added dropwise until 0.1 mL of the solution had been added. This solution was then sonicated in an ultrasonic cleaner (Branson) for 10 min. This procedure was repeated until the desired amount of **1** had been added. The solution was then stirred for 2 h, with slight heating (30 °C) for the first 20 min. The solution was transferred to a volumetric flask and water was added slowly while mixing to replace evaporation. The solution was then stirred while heating in a water bath at 40–50 °C for 1 or 2 h and then stirred at room temperature overnight. Finally, the solution was filtered with Milipore filters (HA, 0.45 μm) to yield clear solutions.

The solubilization of **1** and **1a** in dipalmitoyl-L-α-phosphatidylcholine vesicles (DPPC) was accomplished using the following procedure. DPPC was added to a test tube as a standard solution in benzene. Then **1** or **1a** was added as a standard solution in methylene chloride or pyridine, respectively. The solutions were mixed together, and the solvent was evaporated by a stream of nitrogen. The tube was then placed under a vacuum for 2 h. Water was added to give a final surfactant concentration of 2.6×10^{-3} M. This mixture was then sonicated for 4 min without a water bath using a Heat System-Ultrasonics, Inc. Sonicator/Cell Disruptor (Model W220F), equipped with a titanium microtip. This warmed the sample to approximately 50 °C. Then the sample was sonicated in a room temperature water bath for 10 min. If the solution appeared turbid, it was sonicated for longer periods of time. In all cases the output power was set at 3. The solution was centrifuged (Fisher Scientific) to remove traces of titanium, and finally the solution was milipore filtered (HA, 0.45 μm).

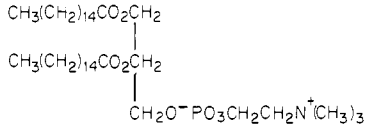
The remaining starting material and porphyrin products were removed from these organized media by extraction. To each sample was added either 2-propanol (in the case of Brij 35 and DPPC) or NaCl (in the case of SDS) to break up the organized media. The aqueous phases were then extracted two or three times with chloroform according to the solubility of the surfactant in this solvent. The chloroform layers were rotary evaporated to dryness with slight heating (25 °C) and the residue was dissolved in a known amount of methylene chloride or chloroform for quantitative analysis. In cases where **1a** was used, the extracted products were converted to methyl esters with diazomethane. The diazomethane was generated by the reaction of *N*-nitrosomethylurea with 50% aqueous potassium hydroxide. The diazomethane was trapped in 0 °C diethyl ether.

Kinetics and Relative Quantum Yields. The relative quantum yields for the photooxidation of protoporphyrin IX (**1** and **1a**) in organized media were obtained by measuring the rate of formation of products **2** and **3** (670 nm) and the rate of disappearance of **1** (507 and 542 nm). Samples were irradiated in the merry-go-round apparatus with 0-52 filters to eliminate all light below 366 nm. All samples were adjusted to the same concentration to assure that the same amount of light was absorbed by both samples. The solutions were irradiated and absorption spectra were obtained in matched cuvettes (Fisher, 100 × 13 mm). Plots of absorbance at 670, 507, and 542 nm vs. time provided straight lines as long as the reaction was followed to only 10% reduction.

Equipment. Irradiations were carried out with a merry-go-round apparatus using a Hanovia 450-W medium-pressure mercury lamp as the light source. Quantitative analysis of the photooxidation products was carried out by using a Perkin-Elmer series I high-pressure liquid chromatograph with a Varian ultraviolet-visible detector. Whatman Partisil PXS 10/25 and 5/25 columns were used with a solvent system of chloroform/hexane (70:30). The products were monitored with the detector set at 420 nm, and the detector was calibrated by using solutions of the photooxidation products synthesized separately as standards. Ultraviolet and visible spectra were recorded on a Perkin-Elmer 576ST spectrophotometer. Fluorescence measurements were carried out by using a Hitachi Perkin-Elmer MPF-2A spectrofluorimeter equipped with a red-sensitive Hamamatsu R446 photomultiplier tube.

Results

Product Studies and Relative Rates. Photoporphyrin IX dimethyl ester (**1**) can be incorporated into SDS, DTAB, and Brij 35 micelles. For these studies precautions were taken to make sure that the porphyrin was not aggregated. This is important so that organized media effects can be separated from any aggregation effects. Brij 35 and DTAB micelles proved better at solubilizing **1** than SDS since some slight aggregation in the SDS micelles remained even after millipore filtering. Protoporphyrin IX (**1a**) can be incorporated into dipalmitoyl-L-phosphatidylcholine vesicles (DPPC) with no aggregation of the porphyrin. The



(DPPC)

concentration of **1** or **1a** in micelles and vesicles was approximately 1.5×10^{-5} M unless stated otherwise.

HPLC was used to obtain the chemical yields and ratios of products for the photooxidation of **1** in the various media. The porphyrins were extracted with chloroform or methylene chloride from these media and concentrated to a small volume before analysis by HPLC. In these studies the concentrations of isomers **2** and **3** were identical within experimental error. At the low concentration used in these studies no diformyldeuteroporphyrin IX (**6**) was observed, indicating that its yield is less than 1%. Table II shows the product yields and the ratios of the two types of products in the various media. The most obvious result is that the ratio of "hydroxyaldehyde" products (**2** and **3**) to the "formyl"

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Table II. Chemical Yields and Product Ratios for the Photooxidation of Protoporphyrin IX in Organized Media

media	% yield (2 + 3)	% yield (4 + 5)	% 1 reacted	ratio of products[a]
SDS[b]	9.1	6.9	74	57:43
Brij 35[c]	8.6	6.3	74	58:42
vesicle[d]	16.8	12.7	83	57:43
Brij 35/D_2O[e]	30.6	9.1	67	77:23
methylene chloride	46.0	1.4	69	97:3

[a] Ratio of (2 + 3):(4 + 5). [b] Sodium dodecyl sulfate micelles. [c] Polyoxyethylene (23) lauryl ether micelles. [d] Dipalmitoylphosphatidylcholine vesicles. [e] Brij 35 micelles in D_2O.

Table III. Relative Quantum Yields for the Photooxidation of Protoporphyrin IX in Organized Media

	$\phi(1)$ organized media[a,c]	$\phi(2 + 3)$ organized media[b,c]
media	$\phi(1)$ CH_2Cl_2	$\phi(2 + 3)$ CH_2Cl_2
SDS[d]	0.76	0.27
Brij 35[d]	0.98	0.67
vesicle[d]	1.39	0.83

[a] Relative quantum yields for the disappearance of 1. [b] Relative quantum yields for the appearance of products 2 and 3. [c] Ratios are calculated at identical concentrations for organized media and methylene chloride solution (1.5×10^{-5} M). [d] These are the same media as in Table II.

products (**4** and **5**) is decreased substantially when the reaction occurs in micelles and vesicles. However, the ratios are not as dramatically shifted from solution as observed for monolayer assemblies.[2] The ratios of products for Brij 35 and SDS micelles and the DPPC vesicles are quite similar.

Another important point to note from Table II is that the total chemical yields of the products thus far identified (**2–6**) are small. The small yields could, in part, be due to the photooxidation or photodegradation of products **2–5**. This was observed for the reaction in organic solvents.[52] However, the total chemical yields are lower in organized media than in organic solvents. This could indicate that the photooxidation of these products is faster in organized media than in organic solvents, but there is no experimental evidence that this is the case. Another possibility is that other products are formed (either through a singlet oxygen or a superoxide path) which do not occur in organic solvents. There are some new peaks in the HPLC chromatogram which have not been previously observed; however, the yield of these products is small (≤5%) and their observance is not always reproducible. The nature of the detection system used here does not allow detection of products which do not absorb strongly at 420 nm. Therefore products of this type would not have been observed.

The relative quantum yields for the photooxidation of **1** in organized media are shown in Table III. In this experiment the quantum yields for the disappearance of **1** and the appearance of products **2** and **3** were calculated relative to the quantum yield in methylene chloride at the same concentration. By having the same concentration in both samples this ensures that the same amount of light is absorbed. This is also important because the quantum yield in solution increases with increasing concentration.[32] The data show that the quantum yields in organized media are not very different from the quantum yield in organic solvents. In fact, these differences are much smaller than the differences in the lifetime of singlet oxygen in methylene chloride (74 μs) vs. the lifetime in water (2–3 μs). There are differences in the values for the various organized media but these are small. One important trend which will be discussed later is the fact that the ratio of quantum yield for products **2** and **3** is smaller than the ratios for the disappearance of **1**.

Replacement of H_2O with D_2O was found to increase the yield of both sets of products for Brij 35 micelles (Table II); the increase in the hydroxyaldehyde products **2** and **3** was much more pronounced than that of the formyl products **4** and **5**.

(52) Cox, G. S.; Bobillier, C.; Whitten, D. G., submitted for publication.

Effect of Quenchers on the Photooxidation. In order to investigate the mechanism or mechanisms operative in the aqueous surfactant solutions, the photooxidation was examined in the presence of several potential quenchers which would be expected to reside either in the aqueous phase, the assembly, or in both. Since a singlet oxygen path is dominant in organic solvents,[32] most of these studies employed quenchers well established as singlet oxygen scavengers. Diazabicyclooctane (DABCO) and cholesterol were used as oxygen quenchers in previous solution studies;[32] however, in the present investigations these quenchers gave somewhat inconclusive results. A major problem with DABCO proved to be its acid–base chemistry and difficulty in determining the solubilization site of DABCO in the aqueous surfactants. A 0.1 M aqueous solution of DABCO has a pH of 10.1, which could affect the rate of the photooxidation without quenching singlet oxygen. A further problem is that the rate constant for DABCO quenching of singlet oxygen is much lower in water than it is in organic solvents.[42] If DABCO (0.1 M) is added with **1** is photooxidized in Brij 35 micelles, the formation of products **2** and **3** is quenched ($\phi^0/\phi = 1.3$). However, reproducible quantum yields were difficult to obtain. In fact, varying the concentration of DABCO from 0.005 M to 0.1 M did not seem to affect the ϕ^0/ϕ values observed.

Cholesterol has proved to be a useful quencher in monolayer assemblies;[2] however, it was of limited utility in the aqueous organized media. When cholesterol was incorporated into DPPC vesicles in a 1:10 mixture (cholesterol:DPPC) some quenching was observed. Exact values for the relative quantum yields (ϕ^0/ϕ) could not be obtained due to the difficulty in obtaining vesicles with reproducible porphyrin concentrations. Since porphyrin concentrations should also affect the quantum yield, comparisons are unreliable. If cholesterol is incorporated into Brij 35 micelles (5×10^{-3} M cholesterol; 3 molecules per micelle) the formation of products **2** and **3** is quenched slightly ($\phi^0/\phi = 1.09$). This value is small and could be 1.0 with experimental error. In fact, if one uses the kinetic scheme for the photooxidation of **1** in organic solvents (see Discussion) and calculates the ϕ^0/ϕ expected for this concentration of cholesterol, a value of 1.0 is obtained. If the quenching effect is real, then it can be explained by the fact that the effective concentration of cholesterol in a micelle is higher than 5×10^{-3} M. At a higher concentration cholesterol would be expected to more efficiently compete for singlet oxygen. This is a major problem with both DABCO and cholesterol. Since k_d for deactivation of singlet oxygen is much higher in water (3.3×10^5 s^{-1}) than in methylene chloride (1.4×10^4 s^{-1}) the concentration of quencher must be higher to effectively compete in quenching.[53] For quenchers with low k_q values such as DABCO ($k_q = 1.4 \times 10^6$ M^{-1} s^{-1})[41] and cholesterol ($k_q = 6.7 \times 10^4$ M^{-1} s^{-1}),[54] the concentrations needed to observe quenching are so high that the presence of these quenchers will affect the environment of the micelle or vesicle.

Sodium azide is an effective quencher of singlet oxygen ($k_q = 5.1 \times 10^8$ M^{-1} s^{-1}) which has been used frequently to study photooxidations in both organized media and in biological systems.[42] When sodium azide is solubilized into solutions of Brij 35 micelles containing **1**, quenching of products **2** and **3** is observed. (In this study the total concentration of sodium was kept constant by the addition of NaCl or excess NaBr.) However, the ϕ^0/ϕ value increased with azide concentration until at high concentrations there was no increase in quenching observed (Figure 1). A more pronounced quenching leveling off at a higher ϕ^0/ϕ value was obtained for Brij 35 in D_2O (Table IV). Results similar to those obtained for Brij 35 in H_2O were obtained for aqueous SDS and DTAB. In the latter system (Figure 2) an increase in the quenching was observed at very high $[N_3^-]$ after the plateau in ϕ^0/ϕ was reached. As will be discussed subsequently, azide ion is expected to reside totally in the aqueous phase for all of the surfactant solutions except DTAB where some attraction to

(53) Merkel, P. B.; Kearns, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 7244.
(54) Doleiden, F. H.; Fahrenholtz, S. R.; Lamola, A. A.; Trozzolo, A. M. *Photochem. Photobiol.* **1974**, *20*, 519.

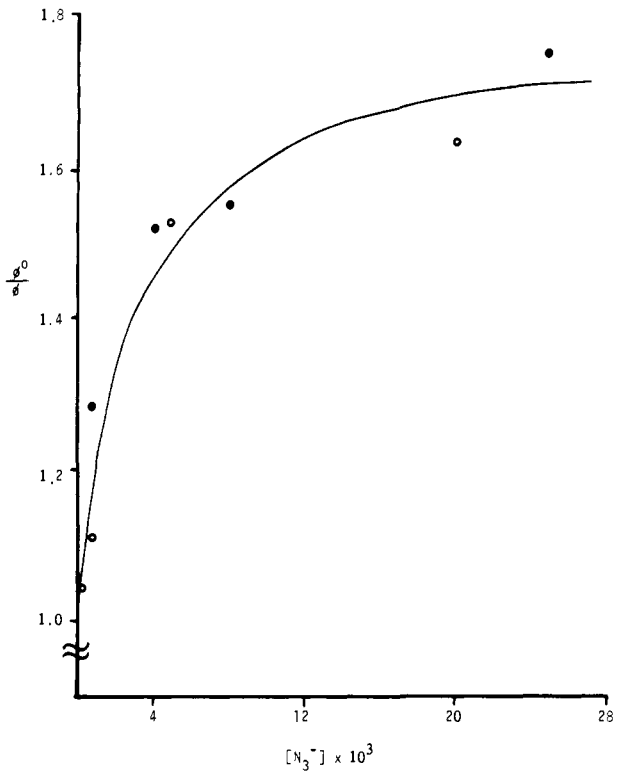

Figure 1. Stern–Volmer plot of the quenching of hydroxyaldehyde formation from **1** in Brij 35 micelles (H_2O) and from **1a** in DPPC vesicles by added azide ion: (●) vesicles; (○) Brij.

Table IV. Intramicellar and Intermicellar Photooxidation of 1 and 1a to Hydroxyaldehyde Products 2 and 3 in Micelles[a]

medium[b]	ϕ^0/ϕ	% intramicellar	% intermicellar
Brij 35/H_2O[c]	1.7 ± 0.1	59	41
Brij 35/D_2O[c]	5.0	20	80
SDS[c]	1.8 ± 0.1		
DTAB[d]	1.7 ± 0.1		
DTAB[e]	1.9 ± 0.1		
vesicles (DPPC)	1.7 ± 0.2		

[a] Porphyrin concentration 1.5×10^{-5} M. [b] Aqueous solution with N_3^- added as quencher. [c] 0.065 M surfactant used. [d] 0.1 M DTAB with 0.1 M NaBr. [e] 0.1 M DTAB with 0.03 M [$NaCl_2$ + NaN_3].

the cationic head groups may be anticipated.[55] Thus the leveling off in the plot of ϕ^0/ϕ vs. $[N_3^-]$ can be attributed to a separation of the photooxidation into intra- and intermicellar components.

When azide was used as a quencher of the photooxidation of **1** in DPPC vesicles a similar effect was observed (Figure 1). (In this case azide was present on both sides of the vesicle bilayer.) Because of light scattering which occurs in vesicle solutions, the kinetic observations for these experiments are not as accurate as the studies in micelles. If one point is discarded ($\phi^0/\phi = 2.41$; $[N_3^-] = 0.15$) then the limiting quenching, ϕ^0/ϕ, is approximately 1.7.

Discussion

Prominent features of the photooxidation of protoporphyrins **1** and **1a** in micelles and vesicles include the increase in formyl products **4** and **5** relative to the hydroxyaldehydes **2** and **3**, the effect of changing the "solvent" from H_2O to D_2O on product yields and distribution as well as the differential quenching of the various products by azide ion, a singlet oxygen quencher which would be expected to reside "outside" of the surfactant assembly for most of the systems studied. The fact that azide quenches

(55) Bonilha, J. B. S.; Foreman, T. K.; Whitten, D. G. *J. Am. Chem. Soc.*, in press.

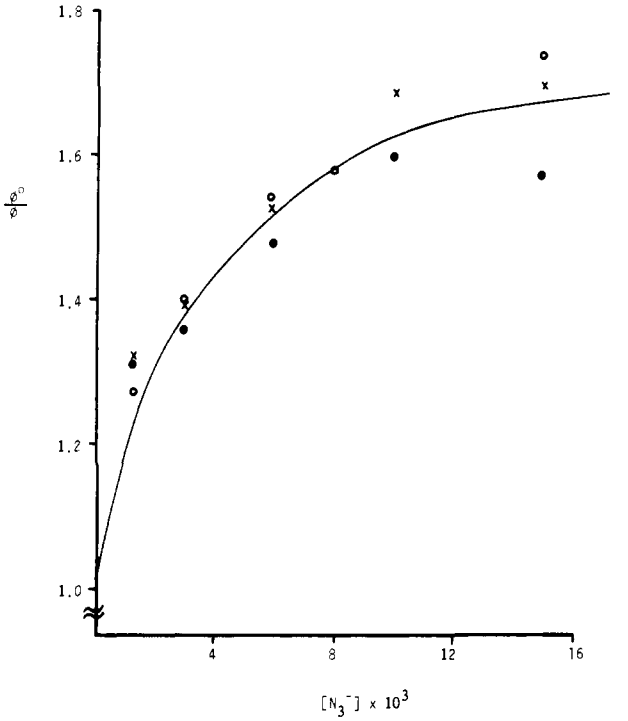

Figure 2. Stern–Volmer plot of the quenching of hydroxyaldehyde formation from **1** in DTAB and SDS micelles by azide ion: (●) DTAB, [NaBr] = 1 M; (○) DTAB, $[N_3^-] + [Cl^-] = 3 \times 10^{-2}$ M; (×) SDS, $[N_3^-] + [Cl^-] = 3 \times 10^{-2}$ M.

only a portion of the reaction and at the same time produces a dramatic change in product distribution suggests that there are at least two paths for reaction in the organized assemblies. In the subsequent discussion we apply a kinetic analysis to clarify the mechanisms for the photooxidation.

Intra- and Intermicellar Singlet Oxygen Paths. It is perhaps useful to focus first on the effects produced by Brij 35 solution upon changing from H_2O to D_2O. In the absence of quencher the overall quantum yield for hydroxyaldehydes **2** and **3**, ϕ^{0HA}, is increased by a factor $\phi^{0HA(D_2O)}/\phi^{0HA(H_2O)} = 3.8$. Since these products were found to be formed in organic solvents exclusively by attack of singlet oxygen on ground-state porphyrin,[32] it is reasonable to assume that the same path applies in the organized assemblies. In several other studies involving photooxidations in aqueous media the substitution of D_2O for H_2O leads to an increase in photooxidation efficiencies; this is usually attributed to a substantial increase in the lifetime of singlet oxygen from H_2O (τ^0 = 2–3 μs) to D_2O (τ^0 = 30–50 μs).[42,48,56] In most cases it has been assumed that the change from H_2O to D_2O produces little change in the rates of other oxidation paths. The quenching of photooxidation products **2** and **3** by azide is substantially more pronounced in D_2O than H_2O; if we assume that the plateau where the quenching levels off (Figures 1 and 2) represents the residual intramicellar reaction unquenchable by azide, we can calculate separately the ratios $\phi^{HA(D_2O)}/\phi^{HA(H_2O)}$ for the intramicellar and intermicellar fractions of the reaction, respectively. This gives

$$\phi^{HA(D_2O)}/\phi^{HA(H_2O)} = 1.3 \text{ (intramicellar)}$$

and

$$\phi^{HA(D_2O)}/\phi^{HA(H_2O)} = 7.4 \text{ (intermicellar)}$$

These results indicate that most of the increase in the quantum yield in D_2O is due to an increase in the intermicellar reaction. The extent of the increase (see below) is reasonable in view of the increase in singlet oxygen lifetime changing from H_2O to D_2O. The fact that the intramicellar ratio is close to 1 indicates that the change from H_2O to D_2O causes little effect on the reaction

(56) Pooler, J. P.; Valenzeno, D. P. *Photochem. Photobiol.* **1979**, *30*, 581.

occurring within the micelle and could be taken as an indication that the porphyrin resides in a relatively hydrophobic site such that singlet oxygen and porphyrin within the micellar "cage" see relatively little water; however, as will be shown below, this is not necessarily the case.

The portion of the photooxidation due to singlet oxygen attack on the porphyrin can be described by eq 2–8. In this scheme

$$P_{mic} \xrightarrow{h\nu} {}^1P_{mic}^* \rightarrow {}^3P_{mic}^* \quad (2)$$

$${}^3P_{mic}^* + {}^3O_{2\,mic} \rightarrow P_{mic} + {}^1O_2{}^*_{mic} \quad (3)$$

$${}^1O_2{}^*_{mic} + P_{mic} \xrightarrow{k_p} \alpha(\mathbf{2} + \mathbf{3}) + (1 - \alpha)\text{other} \quad (4)$$

$${}^1O_2{}^*_{mic} \xrightarrow{k_d} O_2 \quad (5)$$

$${}^1O_2{}^*_{mic} \underset{k_m}{\overset{k_h}{\rightleftharpoons}} {}^1O_2 + M_p \quad (6)$$

$${}^1O_2{}^* \xrightarrow{k_{d'}} O_2 \quad (7)$$

$${}^1O_2{}^* + Q \rightarrow Q + O_2 \quad (8)$$

reactions 2–5 describe the intramicellar events unquenchable by quenchers such as azide residing only in the aqueous phase. Reaction 6 represents the escape and reentry of singlet oxygen from the micellar phase, specifically a micelle containing protoporphyrin. Reactions 7 and 8 are simply decay and quenching processes occurring in the aqueous (H_2O or D_2O) phase. If we assume that quenching of triplet **1** (or **1a**) by oxygen is complete, the yield of steps **2** and **3** should be a constant, β. Using these equations, the quantum yield for formation of **2** and **3** via singlet oxygen in the intramicellar path can be calculated according to eq 9, where [P] represents the effective concentration of porphyrin

$$\phi_{(intra)}^{0HA} = \frac{\alpha\beta k_p[P]}{k_p[P] + k_d + k_h} \quad (9)$$

within the micelle. The quantum yield for the intramicellar reaction in Brij 35 micelles at a total porphyrin concentration of 1.5×10^{-5} M is 2.4×10^{-5}. If we use this value for $\phi_{(intra)}^{0HA}$ in eq 9 together with the α (0.09) and β (0.77) values determined in solution[32] and $k_h = 4.2 \times 10^7$ s^{-1},[38,39] we obtain $k_p[P] = 1.6 \times 10^4$ s^{-1}. The effective concentration of porphyrin within the micelle can be calculated as developed by Mukerjee[57] using eq 10. In

$$[P]_{eff} = \frac{\text{mol of } \mathbf{1}}{V_m([M_p]/[M])} \quad (10)$$

this case the moles of porphyrin are divided by the total micellar volume (V_m) times the fraction of micelles that contain porphyrins ($[M_p]/[M]$). The micellar volume can be calculated by knowing the total volume (V_0), the concentration of surfactants that are involved in micelle formation ([Brij 35] – cmc), the partial specific volume of micellar surfactants (V_s) and the molecular weight of the surfactant (M) (eq 11). V_s is approximately 1.0, so the

$$V_m = V_0([\text{Brij 35}] - \text{cmc})V_sM \quad (11)$$

effective porphyrin concentration is 2.1×10^{-2} M.[57] Using this concentration, the value for k_p in Brij 35 micelles is equal to 7.6×10^5 M^{-1} s^{-1}. This value is remarkably similar to k_p in methylene chloride ($k_p = 8.5 \times 10^5$ M^{-1} s^{-1}).[32]

From the above discussion it appears that the intramicellar reaction of excited porphyrin with oxygen and subsequent reactions (eq 4 and 5) occur about as readily as in solution. The main factor giving a relatively low intramicellar quantum yield (despite the high effective [P]) is the rapid escape of singlet oxygen from the micelle (k_h, eq 6). The fraction of excited singlet oxygen that escapes from the micelles is given by eq 12. Since k_h is much

$$F = \frac{k_h}{k_p[P] + k_d + k_h} \quad (12)$$

(57) Mukerjee, P. *J. Phys. Chem.* **1962**, *66*, 1733.

Table V. Calculated and Experimental Values for the Intermicellar Quantum Yield of Hydroxyaldehydes 2 and 3 in Brij 35 Micelles

	H_2O[a]	D_2O[b]
ϕ^0_{intra} (exptl)	2.4×10^{-5}	3.1×10^{-5}
B	0.108	0.643
ϕ^0_{inter} (exptl)	1.67×10^{-5}	1.24×10^{-4}
ϕ^0_{inter} (calcd)	2.9×10^{-6}	5.6×10^{-5}

[a] Assuming $\tau = 3$ μs. [b] Assuming $\tau = 50$ μs.

larger than k_d for any of the possible environments of the porphyrin–oxygen pair (hydrocarbon, D_2O, H_2O), it is clear that the effect of replacing the H_2O with D_2O should not influence the intramicellar ϕ^{0HA} and that the ratio given above should be, within experimental error, unity as found.

The most probable intermicellar path for singlet oxygen involves its escape from the originating micelle, an excursion through the aqueous medium, and reentry into a micelle containing porphyrin. An approximate expression for the efficiency for this occurring on the first escape from the originating micelle is given by eq 13,

$$E \approx \beta \underbrace{\left(\frac{k_h}{k_p[P] + k_d + k_h}\right)}_{(A)} \times \underbrace{\left(\frac{k_m[M_p]}{k_{d'} + k_m[M_p]}\right)}_{(B)} \underbrace{\left(\frac{\alpha k_p[P]}{k_p[P] + k_d + k_h}\right)}_{(C)} \quad (13)$$

where $k_{d'}$ is the rate constant for decay of singlet oxygen in the aqueous (or D_2O) medium.[58] The term A in eq 13 is approximately unity while $\beta \cdot C$ is simply the intramicellar quantum yield $\phi_{(intra)}^{0HA}$ (eq 9) and B is the fraction of singlet oxygen that survives an excursion through the aqueous medium (and micelles not containing porphyrin) to enter a porphyrin-containing micelle. This equation can be simplified to eq 14. However, since the

$$E = \phi_{(intra)}^{0HA} \times \left(\frac{k_m[M_p]}{k_{d'} + k_m[M_p]}\right) \quad (14)$$

sequence of escape and reentry can occur several times due to the low probability of reaction or deactivation in a given micelle, the true intermicellar yield should be given by eq 15. Equation 15

$$\phi_{(inter)}^{0HA} = \phi_{(intra)}^{0HA} \times B[1 + B + B^2, ..., B^n] \quad (15)$$

can be approximated by a simpler mathematical expression, eq 16, which can be evaluated for the reaction in both Brij 35–H_2O

$$\phi_{(inter)}^{0HA} = \phi_{(intra)}^{0HA} \times B\left(\frac{1}{1 - B}\right) \quad (16)$$

and Brij 35–D_2O. Table V gives values thus calculated and compares them with the measured values. For both D_2O and H_2O the measured values are somewhat (2–6 times) higher than those calculated. While the lack of agreement is probably not too serious, it is possibly worthwhile to consider sources of the discrepancy. Clearly the major source lies in term B as defined above and in eq 14; it appears that B, as calculated, is too small. Since it seems unlikely that the $k_{d'}$ values for H_2O and D_2O are incorrect or that $k_m[M_p]$ is much larger than the values used, a major source of error may be in the model which is based on the assumption that intermicellar exchange involves diffusion of "free" singlet oxygen through the aqueous phase. Since the lifetime of singlet oxygen is longer in hydrocarbon solvents and it is also more soluble in organic solvents, one possibility is that at least a portion of the intermicellar exchange occurs through transfer via submicellar units containing some surfactant and $O_2{}^1*$. On the other hand.

(58) This expression is approximate since it reflects decay of $^1O_2{}^*$ after it enters micelles not containing porphyrin. Since most of the $^1O_2{}^*$ entering micelles will exit, this omission will be unimportant until extremely high surfactant concentrations are employed.

Table VI. Values for the Stern-Volmer and Quenching Constants for Azide Quenching of Intermolecular Formation of 2 and 3 in Surfactant Solutions

medium	k_{sv}, M^{-1}	τ, μs	k_q, M^{-1} s^{-1}
Brij 35-H_2O	754[a]	3	2.5×10^8
Brij 35-D_2O	6125[a]	30	2.0×10^8
DTAB-H_2O[b]	605[a]	3	2.0×10^8
DTAB-H_2O[c]	492[a]	3	1.6×10^8
SDS-H_2O	566[a]	3	1.9×10^8
DTAB,[b,c] SDS-H_2O	623[d]	3	2.1×10^8

[a] Plotted from $\phi_{inter} = \phi_{tot} - \phi_{intra}$. [b] Cl^- added to keep ionic strength constant. [c] Excess Br^- added. [d] Extrapolated from computer curve-fitting procedure.

the ratios of the quantum yields for the intermicellar process (eq 16) for H_2O and D_2O give eq 17; the actual quantum yield ratio

$$\frac{\phi^{0HA}_{(inter)}(D_2O)}{\phi^{0HA}_{(inter)}(H_2O)} = \frac{k'_d(H_2O)}{k'_d(D_2O)} \tag{17}$$

is 7.4 which is in fair agreement with the values of 10–17 obtained using literature values[41] for the right-hand ratio.

Examination of the intermicellar reaction in the presence of the aqueous-phase quencher N_3^- leads to eq 18, analogous to eq

$$\phi^{HA}_{(inter)} = \phi^{0HA}_{(intra)} \times B_q\left(\frac{1}{1 - B_q}\right) \tag{18}$$

16, where $B_q = k_m[M_p]/(k_{d'} + k_q[Q] + k_m[M_p])$. The ratio of eq 16 to eq 18 gives a Stern–Volmer type relationship, eq 19,

$$\phi^{0HA}_{(inter)}/\phi^{HA}_{(inter)} = 1 + k_q\tau^0[Q] \tag{19}$$

predicting linearity between the quantum yield ratio and azide concentration. Reasonable linear plots are obtained for both Brij–D_2O and Brij–H_2O as well as for aqueous solutions of **1** in DTAB and SDS. Values for k_q extracted from these plots or by a curve-fitting procedure are listed in Table VI. Interestingly, all of the surfactant solutions give the same value, $k_q = 2 \times 10^8$ M^{-1} s^{-1}, within experimental error, a value in close agreement with other determinations for azide quenching or singlet oxygen in aqueous surfactant solutions.[41,42]

In summary, the singlet oxygen-induced photooxidation of **1** in the organized assemblies studied can be separated into two components, an intramicellar portion and an intermicellar one. The latter process is largely limited by decay of singlet oxygen in the aqueous phase. Overall, the singlet oxygen path appears kinetically similar to the same reaction in homogeneous solution except for the separation. However, the occurrence of the intramicellar path leads to a more complex concentration dependence than occurs for homogeneous solution. The total quantum yield for singlet oxygen products **2** and **3** is given by eq 20; however,

$$\phi^0 = \phi^0_{intra} + \phi^0_{inter} \tag{20}$$

at low porphyrin concentrations there is only a maximum of one porphyrin per micelle. Therefore the value for [P] within the micelle is constant and the intramicellar quantum yield will be independent of total porphyrin concentration. From eq 15, 16, and 20 it can be seen that the overall quantum yield is given by eq 21 and consists of a concentration-independent term and one

$$\phi^0 = \phi^0_{intra}(1 + (constant)[M_p]) \tag{21}$$

which is approximately linear with M_p at low surfactant and porphyrin concentrations.[59] The intramicellar reaction thus resembles a "cage" process similar to that observed by Stevens[60] in the self-sensitized photooxidation of diphenyl benzofuran in homogeneous solution.

Other Paths for Photooxidation in Aqueous Surfactants. As pointed out previously, a pronounced increase in the ratio of products **4** and **5** to **2** and **3** is a characteristic feature of the change from homogeneous solution to the various organized media studied. Table VII summarizes relative efficiencies of formation of **4–6** in the media studied.

Table VII. Relative Quantum Yields for Formyl Products 4–6 in Solution and Various Organized Media

medium	$\phi^{rel}_{(4-6)}$
SDS-H_2O	10.7
Brij 35-H_2O	13.7
Brij 35-D_2O	21.4
DPPC-H_2O	20
CH_2Cl_2	1.0

Table VIII. Comparison of Quantum Efficiencies for Formation of Formyl Products 4–6 in the Presence and Absence of Azide

medium	ϕ^0_{4-6}	ϕ_{4-6}[a]
Brij 35-H_2O	3.0×10^{-5}	3.5×10^{-5}
Brij 35-D_2O	4.7×10^{-5}	6.3×10^{-5}
SDS-H_2O	2.3×10^{-5}	9.2×10^{-5}

[a] $[N_3^-] = 0.025$ M.

Thus comparison of data in Tables I and III indicates that while the yield of **2** and **3** is slightly lower in SDS, Brij 35 and DPPC vesicles, the quantum yield of **3** and **4** is actually increased in these media compared to CH_2Cl_2 by factors of 10–20. In the studies of the photooxidation in organic solvents it was shown that **4** and **5** are minor products from the singlet oxygen path but that they can also be formed via other pathways, particularly a porphyrin cation–superoxide anion path outlined in eq 22–24.[32] That the

$$P^{3*} + O_2 \rightarrow P^+ + O_2^- \tag{22}$$

$$P^+ + O_2^- \rightarrow \mathbf{4} \text{ and } \mathbf{5} \tag{23}$$

$$P^+ + O_2^- \rightarrow P + O_2 \tag{24}$$

major path for formation of **4** and **5** in the organized media studied does not involve singlet oxygen directly is indicated rather clearly by two results. First for Brij 35 (Table II), it was found that changing the aqueous environment from H_2O to D_2O, which should increase the lifetime of singlet oxygen, the ratio of (**2** + **3**):(**4** + **5**) is significantly increased. Thus while there is a slight increase in the quantum yield for (**4** + **5**) under these conditions, the much smaller increase compared to that for the hydroxyaldehydes suggests that in the organized media **4** and **5** are once again minor products from singlet oxygen. The second result emphasizing the likely role of alternate paths in the formation of **4** and **5** is that addition of azide, a singlet oxygen quencher, decreases the yield of **2** and **3** but actually causes an *increase* in the yield of **4** and **5** (Table VIII). This increase is relatively small for Brij 35 micelles but rather pronounced for SDS.

The first observation above suggests that the alternative path to singlet oxygen attack on **1** in the organized media is largely an intramicellar (or intravesicular) path; this conclusion is reinforced by the observation that quenching of the intermicellar reaction in Brij 35 produces relatively little change in the yield of **4** and **5**. In the absence of quenching the most reasonable intramicellar path for formation of **4** and **5** would be the electron transfer quenching to produce superoxide as outlined in eq 22–24. There is substantial evidence that most, if not all, micelle binding sites are moderately polar such that an electron transfer path to form the separated ions (eq 22) could be enhanced for all the media studied.[61–63] Thus while net quenching via electron transfer may or may not be enhanced relative to energy transfer (eq 3), the net efficiency of product formation (eq 23) vs. back electron transfer (eq 24) could be reasonably anticipated to be enhanced

(59) This assumes B (eq 13) is small and hence $B\alpha[M_p]$ and $1 - B \approx 1$.
(60) Stevens, B.; Ors, J. A.; Pinsky, M. L. *Chem. Phys. Lett.*, 1974, *27*, 157.
(61) Schanze, K. S.; Mattox, T. F.; Whitten, D. G. *J. Am. Chem. Soc.* **1982**, *104*, 1733.
(62) Foreman, T. K.; Sobol, W. M.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 5333.
(63) Russell, M. C.; Whitten, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 3219.

in a polar environment, regardless of whether the host surfactant is neutral or negatively or positively charged.

The enhanced production of **4** and **5** in the presence of azide ion could be attributed to the fact that one path for azide quenching can involve production of superoxide (eq 25) as recently

$$N_3^- + O_2{}^{1*} \rightarrow O_2^{-\cdot} + N_3\cdot \qquad (25)$$

demonstrated.[64,65] Thus in the aqueous media rapid protonation of the superoxide ion followed by disproportionation could produce H_2O_2. In experiments using a 360-nm cutoff filter, we have found that irradiation of solutions containing micellar (SDS) **1** and H_2O_2 leads to enhanced production of **4**, **5**, and **6**.[66] The reason for the enhancement of **4–6** in the presence of azide in SDS compared to Brij 35 remains undetermined.

The increased prominence of the electron transfer path for photooxidation in the organized media used in this study is noteworthy. It is not unreasonable that the behavior observed here should be quite general and perhaps indicative of similar effects in biological photooxidations occurring in various membrane protein environments. It is reasonable to anticipate that generation of superoxide on H_2O_2 in such environments could give rise to extremely complicated reaction sequences. It is tempting to suggest that the differences observed in this study on changing from a homogeneous organic solvent to aqueous surfactant assemblies parallel to some extent the differences between well-characterized singlet oxygen photooxygenations and "photodynamic action" in biological systems. The similarity of results obtained with the various micellar media and the vesicles formed from the natural lipid DPPC suggest that, at least in this instance, the micelles provide an environment similar to that for the lipid portion of biomembranes. We are currently extending these studies to other vesicle systems and to media containing other substrates susceptible to sensitized photooxidation.

(64) Harbour, J. R.; Issler, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 903.
(65) Foote, C. S. *Org. Chem. (N.J.)* **1979**, *40*, 139.
(66) There is no discernible reaction between micellar **1** and H_2O_2 in the absence of light.

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Triplet-to-Singlet Cyclopropylidene–Allene Rearrangement. A Molecular Example of Spin Angular Momentum Coupling in Orthogonal π Systems

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Abstract: Valence-bond and molecular-orbital theories are used to support each other in showing the feasibility of triplet-to-singlet cyclopropylidene–allene rearrangement. It is shown that the symmetry of the orbitals involved and the symmetry of the spin–orbit interaction operators demand an orbitally rotated state corresponding to an orthogonal allene, so as to have a nonvanishing spin–orbit matrix element. As a result, singlet *orthogonal* allene will have a favorable transmission coefficient from triplet cyclopropylidene. This is believed to be general in all perpendicular π-electron systems. Use is made of Hückel–Möbius orbitals for *both* the reactant and the product, to ensure symmetry correlation and orbital following. In addition, a method is devised to correlate an *individual* electron in a spin orbital that circumvents the conventional restriction of having to correlate a spatial orbital with *both* of the two electrons at once. This method simultaneously accounts for molecular-orbital configuration interaction and ensures the correct dissociation limit. It is also postulated that the intermediate state involves angular momentum coupling of two triplets containing a total of four electrons. The resultant singlet-state function correlates well with that of the two orthogonal π bonds of the product allene.

Cyclopropylidene has been of interest for a long time.[1] Its rearrangement into allene has been studied theoretically and experimentally until most recently.[2-11] These include ab initio, MINDO and INDO, etc. The interest lies not only in its place in carbene chemistry[12,13] but also in its rearrangement mechanism.[14] So far, singlet cyclopropylidene to singlet (especially planar) allene has been more thoroughly studied and understood. And it is generally accepted that opening of triplet cyclopropylidene to triplet (planar) allene is a forbidden process.[2] Little work appears to exist on the triplet-to-singlet rearrangement. We propose here to show by a combination of valence-bond and molecular-orbital arguments that the ring-opening rearrangement of triplet cyclopropylidene to *orthogonal* singlet allene is a symmetry-allowed and -favored process. This, we shall show, is because of the unique spin–orbit interaction leading to the perpendicular π-electron system of allene. We shall make use of the symmetry of spin and orbital angular momentum operators,[15-20] symmetry of spin functions,[23,24] Hückel and Möbius orbitals,[21,22] and the orbital following the idea of Zimmerman.[21,25]

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